UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,766	03/15/2007	Stefan Beissert	293024US0PCT	5945

22850 7590 07/21/2009

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER
LONG, SCOTT

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
07/21/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,766	BEISSERT ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 11 May 2009.

Claim Status

Claims 75-94 are pending. Claims 1-74 are cancelled. Claims 75-94 are newly added. Claims 75-94 are under current examination.

Election/Restrictions

The applicant has cancelled all claims pending in the last action and which were subject to a restriction requirement. The new claims read on the elected group and species. The examiner acknowledges the applicant's request for rejoinder of non-elected groups, and additional species, once an indication of allowability for the elected group has been deemed proper. The examiner believes that the applicant is ineligible for rejoinder of additional groups, since claims directed to those groups have been cancelled. However, the species election requirement may be considered at the time of allowance.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. The applicant has indicated that page 3 of the preliminary amendment filed August 13, 2007 contains a statement that the Computer Readable Form (CRF) and the Sequence Listing are identical. Therefore, the examiner finds the application is compliant with 37 CFR 1.821(f).

The examiner had previously noted that the dates on which the Sequence Listing was submitted resulted in the examiner denying priority to the application with the earliest possible date. Upon further consideration, the examiner has reconsidered this position. SEQ ID NO:1 is a polynucleotide encoding human IL-15. This molecule was known in the art, prior to the filing of the earliest priority document for this application. Introducing a sequence listing into the application which contains the sequence of a known molecule (i.e., human IL-15) is not new matter, because the applicant had described using IL-15 in their methods. Consequently, the examiner views this application as fully compliant with the Sequence Rules and hereby withdraws the objection to the specification, based upon non-compliance with the Sequence Rules.

Priority

This application claims benefit from International U.S. Application No. PCT/EP04/13907, filed 7 December 2004 and Foreign Application, EPO 03029899.6 (filed 29 December 2003). Therefore, the instant application has been granted the benefit date, 29 December 2003 from the Foreign Application, EPO 03029899.6

RESPONSE TO ARGUMENTS

35 USC § 112 (written description)

The rejection of claims 24-26, 33-44, 51-59 and 72-74 under 35 USC 112, 1st paragraph (written description) is withdrawn in response to the applicant's arguments and/or claim amendments.

The applicant has cancelled claims 1-74. Therefore, the written description rejection is moot.

Therefore, the examiner hereby withdraws the rejection of claims 24-26, 33-44, 51-59 and 72-74 under 35 USC 112, 1st paragraph (written description).

35 USC § 112 (lack of enablement)

The rejection of claims 24-26, 33-44, 51-59 and 72-74 under 35 USC 112, 1st paragraph (lack of enablement) is withdrawn in response to the applicant's arguments and/or claim amendments.

The applicant has cancelled claims 1-74. Therefore, the lack of enablement rejection is moot.

Therefore, the examiner hereby withdraws the rejection of claims 24-26, 33-44, 51-59 and 72-74 under 35 USC 112, 1st paragraph (lack of enablement).

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112 (lack of enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

NATURE OF THE INVENTION

The breadth of the claims encompasses gene therapy methods of stimulating hair growth by administering a polynucleotide comprising SEQ ID NO:1 operably linked to a keratinocyte specific promoter.

GUIDANCE & WORKING EXAMPLES

The specification does not provide guidance for or a working example for gene therapy methods of stimulating hair growth by administering a polynucleotide comprising SEQ ID NO:1 operably linked to a keratinocyte specific promoter, as required by claim 1. In addition, the specification does not provide guidance for or a working example for gene therapy methods of stimulating hair growth or for ameliorating hair loss by administering a composition comprising a saponin and a polynucleotide construct comprising SEQ ID NO:1 operably linked to a keratinocyte specific promoter, as required by claim 93. The absence of working examples directed to these gene therapy methods necessitates further experimentation. Therefore, the specification does not provide sufficient guidance on how to make and use the instantly claimed methods.

Much of the instant specification is directed to a transgenic mouse which overexpresses IL-15 in the epidermis by means of a keratin K14 promoter (Spec,

Example 2, page 24, parag. 1). Writing about the transgenic mice, the specification states "[i]n this context it should be emphasized that IL-15 will not merely prevent apoptosis but also stimulate and promote growth of the cells" (page 10, lines 19-20). In the context of a transgenic animal as described (and claimed), every cell in the body which expresses keratin K14, would also overexpress IL-15 in these same cells. In such animals, the applicants seem to be able to restimulate growth of keratinocytes at the site of hair follicles. However, this type of delivery and overexpression in every keratinocyte will not be occur in a gene therapy approach comprising administering (in vitro or ex vivo) polynucleotide constructs comprising the gene for IL-15 operably linked to a keratinocyte specific promoter. The transgenic mouse is not an adequate equivalent for topically delivered gene therapy methods.

Regarding the scope of the polynucleotide sequences, there are no working examples of nucleic acids that have been isolated through the stringent hybridization method.

STATE OF THE ART & QUANTITY OF EXPERIMENTATION

The nature of the invention is gene therapy and the state of the prior art is not well developed and is highly unpredictable. Verma et al (Nat. 1997 Sep; 389:239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine

experimentation. Eck et al. (Phar Basis Ther 1995; 77-101) explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. (paragraph bridging pages 81-82) Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3).

In the instant case, the Specification's examples describe a transgenic animal, which expresses IL-15 under the control of a keratinocyte promoter. The transgenic animal model has "solved" the problem of delivery and sufficiency of expression by incorporating the gene everywhere it needs to be (i.e., keratinocytes) and using a promoter which is highly expressed at its desired target tissue (i.e., through incorporation into the genome). The specification does not provide examples for the claimed scope.

Specifically, Danilenko et al. (Molecular Medicine Today. November 1996; pages 460-467) indicates the state of the art regarding stimulating hair growth by topical gene therapy methods is not well developed and poses the question, "can genes encoding growth factors or cytokines be delivered topically such that sustained and therapeutic

levels of protein are produced locally within or near hair follicles?" (page 466, last sentence). In addition, Danilenko et al. teach "In the realm of topical delivery alone, further research into and development of new formulation for the delivery of proteins and genes will be necessary before the safe, effective and sustained delivery of growth factors or cytokines to hair follicles for the treatment or prevention of alopecia becomes a reality." (page 467, last sentence).

The applicant has provided comments directed to Danilenko and the issue of enablement of his claimed invention. The applicant states, "the OA cited Danilenko as describing possible gene therapy impediments, other in the art recognize the promise of follicular gene therapy as shown by Ohyama et al., J. Investig. Dermatol. Symp. Proc. 8(2); 204 (attached 2003) and Verma et al., Nature 389: 239 (1997; of record). Thus, it would have been well within the skill of the art to select a suitable type of gene therapy for use within the context of the present invention" (Remarks, page 10, lines 16-20). The abstract of Ohyama follows:

> Skin and appendages such as hair follicles are attractive candidates for gene therapy targets because they are easily accessible and can be removed and genetically manipulated in culture. Hair follicles are of special interest because our understanding of hair follicle biology and pathophysiology has progressed significantly in recent years, and we now have a much better understanding of how genes, encoding transcription factors, growth factors, and cytokines regulate both hair follicle development and the cycles of hair follicle growth (anagen, catagen, and telogen) (Cotsarelis and Millar, 2001; Millar, 2002). Also important is the characterization of an increasing number of genetic mutations that affect hair growth and can result in hair loss (Cotsarelis and Millar, 2001). Gene therapy could be used to introduce genes that manipulate hair follicle growth and cycling or that replace the mutated defective gene with a normal wild-type gene. As our understanding of the polygenic basis for a number of alopecias improves, gene based therapies might also be designed to provide more promising treatments than current palliative therapies for hair loss. This review will describe some of the recent progress in gene delivery to hair follicles and discuss examples of how gene delivery can cause phenotypic changes in hair follicles.

It is clear that Ohyama merely provides motivation or suggestion to perform a genus of methods encompassing the applicant's claims. There is nothing in the teachings of Ohyama which indicate the claimed method is predictable and could be successfully practiced by a skilled artisan. Verma does not mention skin, hair, follicle, keratinocytes, or IL-15. Therefore, the examiner does not believe that the "promise" suggested by the art mentioned by the applicant is sufficiently enabling for the claimed methods.

The applicant seems also to suggest that transgenic animals comprising keratinocyte specific expression of IL-15 is enabling for stimulating hair growth by topical or *ex vivo* administration of a composition comprising a polynucleotide construct comprising SEQ ID NO:1 operably linked to a keratinocyte specific promoter. This has been discussed above. The examiner finds the applicant's arguments unpersuasive.

CONCLUSION

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the guidance and working examples provided, and the breadth of the claims that it would require undue experimentation to practice the invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner, Art Unit 1633
/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633